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INOTREM control innate immunity

Novel immunotherapies for life-threatening inflammatory syndromes

Inotrem is developing novel immunomodulators that target the TREM-1 pathway. The company's lead compound, nangibotide, is a first-in-class anti-TREM-1 peptide and is currently in phase 2 trials for septic shock.

An excessive immune response is often responsible for the fatal damage caused by conditions such as septic shock, a major public health issue for which effective treatments are lacking. Enter Inotrem, a Paris-based biotechnology company that specializes in controlling the over-reactive immune response by targeting the underlying cause: the disproportionate activation of the triggering receptor expressed on myeloid cells 1 (TREM-1) pathway.

TREM-1 is an immune receptor expressed by myeloid and endothelial cells. Inotrem has discovered that, when activated, TREM-1 can escalate an inflammatory response, causing excessive and damaging inflammation and hemodynamic imbalance. "TREM-1 could be viewed as a new immune stimulatory checkpoint," said Jean-Jacques Garaud, co-founder and CEO of Inotrem. "We have harnessed our significant expertise in TREM-1 pathway biology to develop a proprietary technology platform against this important target."

Inotrem, which was founded in 2013, is developing novel immunomodulators that target the TREM-1 pathway. Its lead compound, nangibotide, is a first-in-class anti-TREM-1 peptide that prevents the protein–protein interaction between the TREM-1 receptor and its agonist ligand (**Fig. 1**). "Nangibotide controls the amplification loop of the inflammatory response, but does not eliminate it entirely, therefore it is a true immunomodulator, not an immunosuppressive," explained Garaud. "It has potential applications in a number of therapeutic indications for which there is huge unmet need, including septic shock and myocardial infarction."

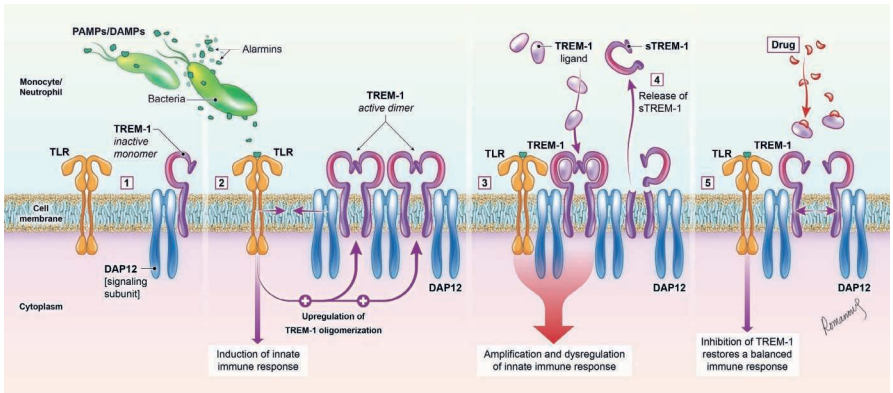

Fig. 1| Inside the TREM-1 pathway. Iconography for the mechanism of activation of the TREM-1 pathway (left) as well as the molecular mechanism of action of nangibotide (right). DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; sTREM-1, soluble triggering receptor expressed on myeloid cells 1; TLR, toll-like receptor.

Septic shock

Sepsis, the tenth leading cause of death in developed countries and the first in critical care units, is characterized by an intense and excessive systemic inflammatory reaction in response to a serious infection. Septic shock, the ultimate complication of sepsis, is a very serious and debilitating acute condition that has high mortality and is associated with long-term physical, psychological and cognitive disabilities in survivors. "Hyperactivation of the TREM-1 pathway is responsible for the onset and progression from sepsis to septic shock," said Garaud. "By targeting the mechanism involved, nangibotide has the potential to reverse shock and improves patient survival."

In seven preclinical models in four different species, nangibotide has been shown to restore an appropriate inflammatory response and vascular function, and improve survival rates, even when administered up to 24 hours after onset of infection. Clinical studies to date show that intravenously administered nangibotide is safe and well tolerated. Its use in septic shock has been granted fast-track status by the US Food and Drug Administration and it is the first critical-care product to be ranked a priority medicine by the European Medicines Agency. The drug is currently in a phase 2b trial for treating septic shock; results are expected by the second half of 2021 (ASTONISH trial, NCT04055909).

In parallel, Inotrem is developing a companion diagnostic with Roche Diagnostics to identify those patients who have high plasma levels of the mechanism-based biomarker, soluble TREM-1, and are most likely to benefit from or respond to nangibotide. "One of the main issues with septic shock is the heterogeneity of this patient population," said Garaud, who was previously head of research and early development at the Roche Group. "Our diagnostic paves the way to a personalized healthcare approach in critical care medicine."

TREM-1 receptors are also found on endothelial cells in tissue-stress situations, and the excessive immune response mediated by TREM-1 has been characterized in ischemia reperfusion injury, myocardial infarction, hemorrhagic shock, pancreatitis and renal failure. Exploiting the numerous capabilities of its proprietary technology platform, Inotrem has generated a large body of data that support the future use of nangibotide in the treatment of acute myocardial infarction, to prevent tissue damage caused by ischemia–reperfusion injury.

Furthermore, with a growing body of evidence implicating the TREM-1 pathway in chronic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, nonalcoholic steatohepatitis and inflammatory bowel disease, the company has launched an anti-TREM-1 monoclonal antibody program targeting chronic inflammatory diseases.

Partnering for development

There is a critical need for therapies that address the root cause of acute and chronic inflammatory syndromes. Inotrem's unique strategy of targeting the TREM-1 pathway could be the new immunotherapy game changer, and pending clinical evidence certainly supports this claim. Inotrem is open to collaboration with private equity firms for further investment and large pharmaceutical companies to advance its late-stage clinical programs. "There are many different areas to explore," said Garaud. "As well as potentially transforming intensive-care medicine, our new way of managing inflammation and our personalized medicine approach could bring targeted therapeutic solutions to a range of other major and underserved public health issues."

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